REMARKS

I. Status of the Claims

Claims 1-40 were filed with the application. Claims 2, 3, 5-8 and 10-40 have been withdrawn from consideration. Thus, claim 1, 4 and 9 are under consideration and have been examined. The claims are rejected under 35 U.S.C. §112, first paragraph (written description and enablement). Additionally, claim 1 is rejected under 35 U.S.C. §102.

II. Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

The examiner has maintained the written description rejection under 35 U.S.C. §112, first paragraph, alleging that there is a lack of a clear description of small molecule inhibitors of NF-AT3. The examiner again cites to the *Lilly* case for the proposition that "an adequate written description of a DNA requires a precise definition." Applicants submit that examiner is attempting to create a rule of law from *Lilly* where none currently exists. *Lilly* and its subsequent cases have ***not*** required that an invention must ***always*** be specifically described as *Lilly* required for those ***particular*** DNA molecules, nor do the cases require that a genus must be described in its entirety, but rather that a genus may be claimed from a representative number of contained species.

Recent cases elaborating on the holdings of *Lilly* show that "the failure of the patent to describe the claimed sequences by anything other than their function" is problematic, but that the proper standard varies depending on the invention and whether it can be described in more than a functional way. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002). Both *Lilly* and *Enzo* require that "the disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim." The important point of both cases is

that function alone, *i.e.*, wishful thinking, cannot support a set of claims to the molecules (or DNA) behind that function. However, it does not set up a proscription against the generic claiming of biological molecules. In this regard, it is thus of utmost importance to note that the present specification does not rely on function alone; specific examples and specific molecules are given so that one of skill in the art would be able to visualize or recognize the subject matter of the claims.

The examiner asserts that "configuration of the second zinc finger of GATA4 ... is not known," and that such lack of knowledge also somehow constitutes a failure of written description. Knowledge of the actual binding site is ***not*** a requirement for one of skill in the art to appreciate that inventors had possession of the claimed invention. Moreover, as discussed in the declaration of Dr. Rick Gorczynski, those of skill in the art would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3's ability to activate gene transcription of hypertrophic genes.

As stated in MPEP §2163, an "objective [of §112] is to put the public in possession of what the applicant claims as the invention." Applicants submit that, unlike the *Lilly* case, where the DNA molecules at issue had not yet been discovered, a number of the NF-AT3 targeting molecules disclosed by applicants ***are already known***, and thus have been sufficiently described to put the public in possession of the invention. This provides yet another important distinction between the instant application and *Lilly*, to which the examiner repeatedly points.

The examiner next asserts that "it is not clear whether DTC's actually bind to NF-AT3, which is a limitation of claims 4 and 9." First of all, "it is not clear" does not carry the

examiner's burden to adduce evidence that the DTC's ***don't*** bind NF-AT3. Second, even if proven, this fact would not create a written description issue as many of the other molecules listed do, however, describe molecules that do bind NF-AT3, and thus satisfy the limits of claims 4 and 9. The written description requirement does not demand exhaustive listings of molecules and detailed description of binding sites and binding regions. Applicants again cite to *Lilly*, which states "a specification may, within the meaning of §112 P1, contain a written description of a broadly claimed invention without describing all species that claim encompasses." This specification goes beyond simply claiming an undescribed molecule, it actually refers to GATA4 mimetics, DTC's, antisense molecules (p. 27, lines 12-20), antibodies, competitive inhibitors of NF-AT3 (p. 30, line 21) as well as other proteins that inhibit NF-AT3 (in addition to Examples 3, 6-9, see Summary of the Invention page 4, lines 15-25). These examples describe specific molecules known in the art and whose mention alone should be sufficient to satisfy the written description requirements of §112.

Furthermore, the examiner complains that antibodies and mimetics are described in a functional way and without detailed description of the actual binding sites. Just as above, applicants note that the examiner appears to be overextending the description requirements of *Lilly*. The specification describes specific molecules that interact with NF-AT3 in a way that goes beyond mere wishful thinking. These molecules are shown to interact, or can be proven with little experimentation to interact, with NF-AT3. That alone is sufficient to describe the invention in a comprehensible way to the public. The mere fact that they are not described atom by atom does not rob the claims of written description.

The above statements, taken in light of *Lilly* and *Enzo* as those courts intended, should successfully traverse the Examiner's rejections for lack of written description. Therefore, Applicants respectfully request that the rejection be withdrawn.

III. Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1, 4 and 9 remain rejected for lack of enablement. The examiner has rejected applicants' prior arguments and again focuses on MPEP §2614.03 as requiring more detail from the specification as how to make and use the invention. The examiner still argues that the art is unpredictable, that the invention has not been enabled by the specification, and that it would constitute "an undue burden" for one of skill in the art to practice the invention. Applicants respectfully traverse this rejection and reiterate that the examiner has misapplied the standard of undue experimentation.

It may be true that the use of NF-AT3 inhibitors to treat hypertrophy is not well-known, but the information provided in the specification, coupled with what was known prior to this invention, would allow one of skill in the art to practice the invention. The examiner's criticism almost seems to rise to the level of requiring a working model, and according to MPEP §2164.02 "an applicant need not have actually reduced the invention to practice prior to filing." It is important to remember that "because only an enabling disclosure is required, applicant need not describe all actual embodiments. The absence of working examples will not by itself render the invention non-enabled. Furthermore, a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled." (MPEP §2164.02). Examples 6 through 9 clearly show *in vivo* proof that use of NF-AT3 inhibitors can be a method to treat hypertrophy.

The examiner has rejected experimental data in the application by asserting that the transfected cells and transgenic mice are not representative of what would be found in human subjects and, thus, that the data are not enabling for use *in vivo* for patients. Applicants again refer examiner to the affidavit of Dr. Rick Gorczynski, regarding the validity of the transfection model and transgenic mouse model. In particular, Ritter *et al.*, *Circulation*, 105:2265-2269, (2002) showed that NF-AT2 is indeed in a dephosphorylated and therefore more active form in hypertrophic heart, as compared to normal human heart. These results provide *in vivo* evidence from a human clinical setting, albeit indirect, that there is an altered NF-AT phosphorlyation state in hypertrophied myocardium. It further validates the notion of targeting NF-ATs therapeutically to combat hypertrophy by interfering with the NF-AT transcriptional cascade. Regarding the issue with transfected cells, applicants refer the examiner to the attached scientific publications Molkentin, J. "The Zinc Finger-containing Transcription Factors GATA-4, -5, and –6" (*J. Biol. Chem.* 275:50, 38949-38952, 2000), and Olson *et al.* "Remodeling muscles with calcineurin," (*BioEssays* 22:510-519, 2000). Based on the results set forth in these manuscripts, it is clear that a person of ordinary skill in the art would recognize that NF-AT3 does indeed interact with GATA-4. Perhaps the best information on this point comes from the Molkentin mini-review, which summarizes the state of the art as of over a year ago. This article states "GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT)." (p. 38951, also see Molkentin, Cell 93, 215; and Morin, *EMBO J.*, 19, 2046). What this review article makes clear is that the current state of the field of cardiac hypertrophy studies accepts that GATA-4 does indeed interact with NF-AT3. See also the Gorczynski Declaration.

Applicants further submit that this rejection goes beyond any reasonable enablement requirements for §112. Applicants refer the examiner to *In re Robins*, 429 F.2d 452 (CCPA 1970) cited by *Lilly*, stating, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." Furthermore, *Robins* holds that a "specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement ... unless there is reason to doubt the objective truth of the statements therein." The *Robins* court also demands that "Section 112 requires nothing more than objective enablement. How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance."

The examiner states that "one of skill in the art would not know how to make and use the claimed method, using the small molecule single chain antibodies." This conclusion runs contrary to the holding in *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988), which states that so long as there is "considerable guidance" in the specification and "all of the methods to practice the invention [are] known" then "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." While more enablement may be required where the art is unpredictable, there is no *per se* rule for a working model. The invention must simply enable one of skill in the art to practice that invention, and there is nothing contained in the current application that goes beyond the capabilities of one of skill in the art (MPEP §2164.01 - "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."). Also instructive is *U.S. v. Telectronics, Inc.* 857 F.2d 778 (Fed. Cir. 1992), that "a patent need not teach, and preferably omits, what is well

known in the art ... the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art."

Applicants assert that the discussion above shows that the rejected claims do in fact enable one of skill in the art to practice the invention. Therefore, it is respectfully requested that the claims be reconsidered and the rejection be withdrawn.

IV. Rejection Under 35 U.S.C. §102

Claim 1 is rejected by the examiner under 35 U.S.C. §102(b) as allegedly being anticipated by the above listed references. For literal anticipation of a claim, "a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ.2d 1618, 1624 (Fed. Cir. 1996).

Applicants assert that every element in claim 1 is not found in any of the prior art references. Claim 1 teaches treatment of ***hypertrophy*** by inhibiting the function of NF-AT3 in a cardiomyocyte using a compound that inhibits the function of NF-AT3. The Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do ***not*** teach, much less suggest treatment of hypertrophy or effects on cardiac structure. They are instead directed towards improving cardiac ***function*** in a post-transplant environment. Additionally, while the McCaffrey and Martinez-Martinez references ***do*** teach that CsA is an NF-AT3 inhibitor, they do not teach the use of an NF-AT3 inhibiting compound to treat hypertrophy.

To the extent that the examiner is arguing inherency, applicants submit that the case law requires that an inherent disclosure "must be certain." *Ex parte McQueen*, 123 USPQ 37 (Bd. App. 1958). There is no evidence from the cited references that hypertrophy had been treated or even analyzed. The prior art specifically deals with transplantation disease and cardiac function after transplant in response to CsA application. The references do not teach a treatment for hypertrophy nor would one of skill in the art be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. Thus, the rejection cannot be certain and therefore fails to meet the standards required for an inherency rejection under 35 U.S.C. §102(b).

As each and every element of claim 1 is not found in the prior art, and as claim 1 is inherently anticipated, applicants therefore respectfully request that the rejection under §102(b) be withdrawn.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should Examiner Davis have any questions regarding this response, she is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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